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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/507,164	CARTLIDGE, SUE ANN	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-38* is/are pending in the application.

4a) Of the above claim(s) *26-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/9/06; 11/21/05; 9/9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 15-38 are pending.

2. Applicant's election with traverse of Group II, Claims 3-5, 8 and 14 (now claims 15-25) drawn to a probe directed to the KDR/Flk-1 epitope Y1214, the probe is an antibody, a kit comprising said antibody and a method of making said antibody, filed 9/27/06, is acknowledged. The traversal is on the grounds that newly submitted claims 26-38, directed to methods of using the probe should be examined with Group II because they are so linked as form a single inventive concept. The special technical feature of claims 15-25 is the probe that binds tyrosine residue of Y1214 of the KDR/flk-1 receptor. The special technical feature of claims 26-38 is also the probe, since claims 26-38 are directed to methods of using the probe. Thus, since claims 15-38 have the same or corresponding special technical feature, they have unity of invention and should be examined together. Even if the Office does not group and examine claims 26-38 with claims 15-25, Applicant request rejoinder of method claims (claims 26-28) that once a claim directed to the probe (claims 15-25) is found allowable (see MPEP 821.04).

This is not found persuasive because of the reasons set forth in the restriction mailed July 28, 2006.

The invention listed as Group II (now claims 15-25) do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

Consistent with the International Search Report, the invention of Group II was found to have no special technical feature that defined the contribution over the prior art of Takahashi et al (of record, EMBO J 20(11): 2768-2778, June 2001; PTO 892).

Takahashi et al teach a method of making a probe such as polyclonal antibody that detects activation of KDR/Flk-1 receptor by VEGF-A and binds tyrosine residue Y1175 of the KDR/Flk-1 receptor. The reference method comprises immunizing an animal such as rabbit with a peptide such as VCDPDKFHYDNTAG surrounding PY1175 and isolating antibody from the animal (see page 2776, col. 1, Rabbit anti-phosphoY1775 polyclonal antibody, in particular). Takahashi et al also teach tyrosine residues (Y) at position 1175 (Y1175) and 1214 (Y1214) of the KDR/Flk-1 receptor are the two major VEGF-A dependent autophosphorylation sites in vitro and in vivo (see abstract, page 2770, col. 1, first paragraph, in particular). Takahashi et al also

teach phosphorylation of Y1175 is via MAP kinase (see page 2771 col. 1, in particular) but phosphorylation of Y1214 is not and suggesting that tyrosine phosphorylation of Y1214 may be important for other signaling pathways of VEGF-A in endothelial cells such as the stimulation of chemotaxis, cell survival, or the regulation of gene expression (see page 2775, in particular). Takahashi et al further teach peptide such as VCDPKFHYDNTAG surrounding the Y1214 (see page 2769, col. 2, Figure 1, in particular) and provides motivation to the skilled artisan to make antibody using said phosphospecific peptide surrounding the tyrosine residue to make antibody that is highly specific and distinguishable from other tyrosine residue and kinase receptors (see page 2774, col. 2, in particular). Takahashi et al teach antibody to phosphotyrosine (anti-PY) is useful for detection of activated KDR/Flk-1, not only in the western blotting but also in histological sections (see paragraph bridging page 2771 and 2772, in particular) and potentially for use alone or in combination with a KDR/Flk-1 tyrosine kinase inhibitor (see page 2774, col. 2, in particular). Although Takahashi et al does not specifically teach antibody to Y1214 of the KDR/Flk-1 receptor, Takahashi et al do in fact teach the epitope surrounding Y1214 such as VCDPKFHYDNTAG, which is identical to the claimed phosphorylated peptide of SEQ ID NO: 1 or the unphosphorylated peptide VCDPKFHYDNTAG of SEQ ID NO: 2. Clearly, one having ordinary skill in the art would have been motivated with the expectation of success from the teachings of Takahashi et al to make antibody that is highly specific to Y1214 of KDR/Flk-1 by substituting the peptide VCDPDKFHYDNTAG surrounding PY1175 as immunogen for the other VCDPKFHYDNTAG surrounding PY1214, then immunizing the animal with said peptide and isolating the antibody from the animal.

Since Applicant's inventions do not contribute a special technical feature when viewed over the prior art, they do not have single general inventive concept and lack unity of invention. Therefore, the requirement of Group 2 (now claims 15-25) and methods of using the product (claims 26-38) is still deemed proper and is therefore made FINAL.

The request for rejoinder of the non-elected methods of using the product (claims 26-38) upon an indication of allowance of the product claims (claims 15-25) is acknowledged. However, no product is allowable at this time.

3. Claims 26-38 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

4. Claims 15-25, drawn to a probe directed to the KDR/Flk-1 epitope Y1214, the probe is an antibody, a kit comprising said antibody and a method of making said antibody, are being acted upon in this Office Action.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) an isolated antibody that detects activation of the KDR/FLK-1 receptor and binds specifically to tyrosine residue Y1214 in KDR receptor (the corresponding tyrosine residue in Flk-1 receptor) wherein the antibody is made by immunizing an animal with a phosphorylated peptide consisting of SEQ ID NO: 1, (2) the said isolated antibody is a monoclonal antibody or a polyclonal antibody, (3) a composition comprising the antibody mentioned above and a carrier, (4) a kit comprising the antibody mentioned above for detecting the activation of the KDR/Flk-1 receptor and reagents for detection assays, (5) a method of generating an isolated antibody that detects activation of the KDR/FLK-1 receptor and binds to tyrosine residue Y1214 in KDR receptor (the corresponding to tyrosine residue in Flk-1 receptor) wherein the method comprises immunizing an animal with a phosphorylated peptide consisting of SEQ ID NO: 1 and isolating the antibody from the animal, (6) a method of generating an isolated antibody that binds to tyrosine residue Y1214 in KDR receptor (the corresponding tyrosine in Flk-1 receptor) wherein the method comprises immunizing an animal with a peptide consisting of SEQ ID NO: 2 and isolating the antibody from the animal, and (7) the method of generating antibody mentioned above wherein the animal is a mammal, **does not** reasonably provide enablement for (1) any isolated "probe" that detects activation of the KDR/Flk-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor as set forth in claims 15, 19, 20 and 21, (2) any peptide "comprising" Y1214 of the KDR/Flk-1 receptor for a method of generating antibody, (3) any peptide such as peptide "comprising" SEQ ID NO: 2 or peptide "comprising" SEQ ID NO: 1 for a method of generating antibody using such peptide, and (4) any composition or pharmaceutical composition comprising any probe mentioned above. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. This rejection encompasses three distinct issues, which will be addressed in turn:

Enablement is not commensurate in scope with claims to make and use any "probe" that detects activation of the KDR/Flk-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor.

The specification discloses only monoclonal and polyclonal antibodies that detect activation of the KDR/Flk-1 receptor. The antibody binds specifically to tyrosine residue Y1214 of the KDR receptor (the corresponding SEQ ID NO) and the corresponding tyrosine residue in Flk-1 receptor (the corresponding SEQ ID NO). The specification discloses a phosphorylated peptide consisting of the amino acid sequence of SEQ ID NO: 1 and a non-phosphorylated peptide consisting of SEQ ID NO: 2, see specification page 11. The specification further discloses a method of making antibody using the peptides mentioned above and methods of detecting the activation of the KDR/Flk-1 receptor by measuring the change or level of phosphorylation or the presence or amount of KDR/Flk-1 receptor expressed on a cell in a sample using antibody made with the peptides mentioned above.

The specification does not teach the structure, i.e., nucleotide sequence or peptide sequence or chemical structure of any "probe" that binds to tyrosine residue Y1214 of KDR or the corresponding Y residue in Flk-1 receptor other than antibody. The specification does not teach any assays that are useful for screening probe and is predictive of success in vivo for a pharmaceutical composition. There is not a single nucleotide probe from the smallest to the largest fragment shows any binding specificity and biological effect useful for a medicament for treatment of cancer. Further, there is a lack of in vivo working example demonstrating that the probe is effective for a pharmaceutical composition for the treatment of cancer, see specification page 4, lines 30. Given the unlimited numbers of probes as encompassed by the claims, it is unpredictable which undisclosed nucleotide probe binds specifically to tyrosine residue Y1214 of

the KDR, the corresponding residue in Flk-1 receptor, in turn, would be useful for detecting activation of KDR/Flk-1 receptor.

The state of the prior art as exemplified by Wallace et al (in Methods in Enzymology 152: 432-439, 1987; PTO 892) is such that determining the specificity of hybridization probes is empirical by nature and the effect of mismatches within an oligonucleotide probe is unpredictable.

Stryer et al (in Biochemistry, Third edition, W H Freeman Company, New York, pages 31-33, 1998; PTO 892) teach that a protein is highly dependent on the overall structure of the protein itself and that the primary amino acid sequence determines the conformational of the protein (See enclosed appropriate pages).

Further, there is a lack of in vivo working example demonstrating any pharmaceutical composition comprising any probe is effective for treating any and all disease. As such, the specification merely extends an invitation to one skilled in the art to further experimentation to arrive at the claimed invention. Since the structure of the probe is not enabled, it follows that any composition or pharmaceutical composition or kit comprising such probe is not enabled.

Enablement is not commensurate in scope with claims to make any antibody that binds specifically to tyrosine residue Y1214 of the KDR/Flk-1 receptor using any peptide "comprising" Y1214 of the KDR receptor or the corresponding tyrosine residue in Flk-1 or any peptide such as peptide comprising SEQ ID NO: 1 or SEQ ID NO: 2 for making antibody.

Even if the probe is limited to antibody such as polyclonal and monoclonal antibody, the specification discloses only two peptides. These peptides consist the amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 2.

The specification does not teach the structure of any and all peptide "comprising" Y1214 of the KDR/Flk-1 receptor. The specification does not teach immunizing an animal with any peptide other than the peptide consisting of SEQ ID NO: 1 or the peptide consisting of SEQ ID NO: 2 would bind specifically to tyrosine residue Y1214 of the KDR receptor, or the corresponding tyrosine residue in Flk-1 receptor. Even if peptide is limited to SEQ ID NO: 1 and SEQ ID NO: 2, the term "comprising" is open-ended. It expands the peptide of SEQ ID NO: 1 or SEQ ID NO: 2 to include additional amino acids at either or both ends. There is a lack of guidance as to which amino acids to be added such that antibody made with such peptide still binds specifically to Y1214 of the KDR (corresponding SEQ ID NO) and the corresponding tyrosine residue in Flk-1 (corresponding SEQ ID NO).

The state of the prior art as exemplified by Kuby et al (Immunology, Second edition, pages 86-96, 1994; PTO 892) is such that immunizing a peptide may result in **antibody binding specificity** that differs from antibody specificity directed against the native full-length polypeptide. Given the numerous peptides and without the structure, it is unpredictable which antibody generated from which "comprising" SEQ ID NO: 1 or SEQ ID NO: 2 that containing unlimited number of amino acids added will have the same binding specificity as an antibody generated from the specific peptide consisting of SEQ ID NO: 1 or SEQ ID NO: 2, in turn, would bind specifically to the tyrosine residue Y1214 of KDR, or the corresponding residue in Flk-1 for detection assays. As such, the specification merely extends an invitation to one skilled in the art to further experimentation to arrive at the claimed invention. Accordingly, an undue amount of experimentation would be required to determine how to practice the claimed invention. Since the structure of the peptide is not enabled, it follows that any composition or pharmaceutical composition or kit comprising such antibody made with said peptide is not enabled.

Enablement is not commensurate in scope with claims to make and use any pharmaceutical composition comprising any probe, any antibody such as any polyclonal or monoclonal antibody mentioned above. The lack of guidance as to the structure and binding specificity of the probe have been discussed supra. The specification fails to provide any working examples, or guidance with respect to the dosages for a medicament for treatment of cancer.

Zhu et al (Investigational New Drugs 17: 195-212, 1999; PTO 892) teach despite high sequence homology (i.e. 85%) between mouse FLK-1 and its human homolog, KDR, none of the blocking anti-KDR antibodies produced cross-reacts with Flk-1. Consequently, tumors grown in mice, which recruit the mouse vasculature, are not appropriate models to evaluate the anti-angiogenesis therapy in vivo (see page 201, col. 2, last paragraph, in particular). Given the unlimited numbers of antibody as encompassed by the claims, the lack of in vivo working example, it is unpredictable which antibody made with which undisclosed peptide binds specifically to the tyrosine residue Y1214 of the KDR, or the corresponding residue in Flk-1 receptor for treating any and all cancer.

For these reasons, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary.

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

7. Claims 15-25 are under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) any isolated "probe" that detects activation of the KDR/Flk-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor as set forth in claims 15, 19, 20 and 21, (2) any peptide "comprising" Y1214 of the KDR/Flk-1 receptor for a method of generating antibody; and (3) any peptide such as peptide "comprising" SEQ ID NO: 2 or peptide "comprising" SEQ ID NO: 1 for a method of generating antibody and method of using antibody generated from such peptide for detecting the activation of such KDR/Flk-1 receptor.

The specification discloses only monoclonal and polyclonal antibodies that detect activation of the KDR/Flk-1 receptor. The antibody binds specifically to tyrosine residue Y1214 of the KDR receptor (the corresponding SEQ ID NO) and the corresponding tyrosine residue in Flk-1 receptor (the corresponding SEQ ID NO). The specification discloses a phosphorylated peptide consisting of the amino acid sequence of SEQ ID NO: 1 and a non-phosphorylated peptide consisting of SEQ ID NO: 2, see specification page 11. The specification further discloses a method of making antibody using the peptides mentioned above and methods of detecting the activation of the KDR/Flk-1 receptor by measuring the change or level of phosphorylation or the presence or amount of KDR/Flk-1 receptor expressed on a cell in a sample using antibody made with the peptides mentioned above.

The specification does not disclose the structure of any "probe" that binds to tyrosine residue Y1214 of KDR or the corresponding Y residue in Flk-1 receptor. A probe without the nucleotide sequence or chemical structure has no structure, much less function. Other than the described antibody mentioned above, the present specification fails to disclose any other probe, let alone a representative number. Since the probe is not adequately described, it follows that a

composition or pharmaceutical composition or kit comprising said probe is not adequately described.

With respect to peptide "comprising" Y1214 of the KDR/Flk-1 or peptide "comprising" SEQ ID NO: 1 or SEQ ID NO: 2 for making antibody, the specification discloses only two peptides. These peptides consist the amino acid sequence of SEQ ID NO: 1 and SEQ ID NO: 2. The term "comprising" is open-ended. It expands the peptide Y1214 of the KDR or the tyrosine in the corresponding Flk-1 receptor to include additional amino acids at either or both ends. The specification does not disclose which amino acids to be added, let alone antibody generated with such undisclosed peptide still maintains its binding specificity to tyrosine residue Y1214 of the KDR/Flk-1 receptor. Likewise, a peptide "comprising" SEQ ID NO: 1 or SEQ ID NO: 2 include additional amino acids at either or both ends of SEQ ID NO: 1 and SEQ ID NO: 2. There is a lack of a written description about the amino acids to be added. Further, the specification does not disclose the structure of any other peptide longer than the disclosed peptides. As such, the method of generating antibody using such undisclosed peptide is not adequately described.

The specification discloses only antibody that binds to tyrosine residue at position 1214 (Y1214) of KDR or the corresponding tyrosine residue in Flk-1, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of "probe" to describe the genus for the claimed product. Other than the two specific peptides mentioned above, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of peptide and antibody made with such peptide to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

9. Claims 15-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "Y1214 of the KDR/Flk-1" in claims 15 and 22 is ambiguous and indefinite because "Y1214" does NOT correspond to the tyrosine residue located at position 1214 in the amino acid sequence of the mature Flk-1 receptor and the corresponding SEQ ID NO, see reference sequences set out in the Terman et al reference disclosed at page 9, lines 25-30 of the specification. As such, one of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 15-20 and 22-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al (of record, EMBO J 20(11): 2768-2778, June 2001; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-153).

Takahashi et al teach a method of making a probe such as polyclonal antibody that detects activation of KDR/Flk-1 receptor by VEGF-A and binds tyrosine residue Y1175 of the KDR/Flk-1 receptor. The reference method comprises immunizing an animal such as a rabbit with a peptide such as VCDPDKFHYDNTAG surrounding phosphorylated Y1175 and isolating antibody from the animal (see page 2776, col. 1, Rabbit anti-phosphoY1775 polyclonal antibody, in particular). Takahashi et al also teach tyrosine residues (Y) at position 1175 (Y1175) and (Y1214) of the KDR/Flk-1 receptor are the two major VEGF-A dependent autophosphorylation sites in vitro and in vivo (see abstract, page 2770, col. 1, first paragraph, in particular). Takahashi et al also teach phosphorylation of Y1175 is via MAP kinase (see page 2771 col. 1, in particular) but phosphorylation of Y1214 is not, suggesting that tyrosine phosphorylation of Y1214 may be important for other signaling pathways of VEGF-A in endothelial cells such as the stimulation of chemotaxis, cell survival, or the regulation of gene expression (see page 2775, in particular).

Takahashi et al further teach peptide such as VCDPKFHYDNTAG surrounding the Y1214 (see page 2769, col. 2, Figure 1, in particular) and providing motivation to the skilled artisan to make antibody using phosphospecific peptide surrounding the tyrosine residue of interest to make antibody that is highly specific and distinguishable from other tyrosine residue and kinase receptors (see page 2774, col. 2, in particular). Takahashi et al teach antibody to phosphotyrosine (anti-PY) is useful for detection of activated KDR/Flk-1, not only in the western blotting but also in histological sections (see paragraph bridging page 2771 and 2772, in particular) and potentially for use alone or in combination with a KDR/Flk-1 tyrosine kinase inhibitor (see page 2774, col. 2, in particular). Takahashi et al also teach carrier such as phosphate-buffered saline (PBS) and composition comprising anti-BrdU and PBS (see page 2776, col. 2, Immunocytochemistry, page 2777, col. 1, first paragraph, in particular). Although Takahashi et al does not teach the specific antibody to Y1214 of the KDR/Flk-1 receptor, Takahashi et al do in fact teach epitope surrounding Y1214 such as peptide VCDPKFHYDNTAG, which is identical to the claimed phosphorylated peptide of SEQ ID NO: 1 and unphosphorylated peptide of SEQ ID NO: 2. Clearly, one having ordinary skill in the art would have been motivated with the expectation of success from the teachings of Takahashi et al to make antibody such as polyclonal antibody that is highly specific to Y1214 of KDR/Flk-1 by substituting the peptide VCDPDKFHYDNTAG surrounding PY1175 as immunogen for the other peptide VCDPKFHYDNTAG surrounding PY1214 as taught by Takahashi et al, then immunizing an animal with said peptide and isolating the antibody from the animal.

The invention in claim 17 differs from the teachings of the reference only in that the antibody is a monoclonal antibody instead of polyclonal antibody.

Harlow et al teach a method of making monoclonal antibody to any antigen of interest. Harlow et al further teach the advantages of monoclonal antibody are that the source of antibody will be unlimited, their binding specificity and their homogeneity (see page 141, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make monoclonal antibody as taught by the Harlow et al using the phosphopeptide VCDPKFHYDNTAG surrounding PY1214 as immunogen as taught by Takahashi et al to produce a monoclonal antibody that detects activation of the KDR/Flk-1 receptor and binds specifically to phosphorylated tyrosine residue Y1214 of the KDR receptor (the corresponding Y residue in Flk-1 receptor). From the combined teachings of the references,

it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Harlow et al teach the advantages of monoclonal antibody are that the source of antibody will be unlimited, their binding specificity and their homogeneity (see page 141, in particular). Takahashi et al teach tyrosine residues (Y) at position 1214 (Y1214) of the KDR/Flk-1 receptor is one of the two major VEGF-A dependent autophosphorylation sites in vitro and in vivo and phosphospecific peptide such as VCDPKFHYDNTAG surrounding PY1214 is useful for making antibody that is highly specific and distinguishable from other tyrosine residue and kinase receptors (see page 2774, col. 2, in particular). Takahashi et al teach antibody to phosphotyrosine (anti-PY) is useful for detection of activated KDR/Flk-1, not only in the western blotting but also in histological sections (see paragraph bridging page 2771 and 2772, in particular) and potentially for use alone or in combination with a KDR/Flk-1 tyrosine kinase inhibitor (see page2774, col. 2, in particular). Once the antigen of interest is selected, the use of that antigen in the known method of Kohler and Milstein will result in the expected hybrid cell lines and the specific monoclonal antibodies. Ex parte Erlich, 3 USPQ2d 1011, 1015 (BPAI 1986). Claims 19-20 are included in this rejection because it would have been obvious to one of ordinary skill in the art at the time the invention was made with the expectation of success to substitute the anti-BrdU in a composition comprising and anti-BrdU and PBS for the polyclonal antibody that binds specifically to PY1214 of KDR/Flk-1 for detection of activation of KDR/Flt-1 receptor as taught by Takahashi et al.

12. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Takahashi et al (of record, EMBO J 20(11): 2768-2778, June 2001; PTO 892) in view of Harlow *et al* (in Antibodies a Laboratory Manual, 1988, Cold Spring harbor laboratory publication, Cold Spring Harbor, NY, pages 139-153) as applied to claims 15-20 and 22-25 mentioned above and further in view of US 6,204,011 (filed June 17, 1998; PTO 892).

The combined teachings of Takahashi et al and Harlow et al have been discussed supra.

The invention in claim 21 differs from the teachings of the references only in that a kit for comprising a probe that detects activation of the KDR/Flt-1 receptor and binds tyrosine residue Y1214 of the KDR/Flk-1 receptor.

The '011 patent teaches a kit comprising antibodies that bind to human KDR and all the essential reagents required to perform various assays such as detection assays specific for commercial expedience (see col. 21, lines 65-66, col. 22, lines 5-12, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the antibody that binds to KDR in the kit as taught by the '011 patent for the polyclonal antibody that binds to Y1214 of the activated KDR/Flk-1 receptor as taught by Takahashi et al or the monoclonal antibody that binds to Y1214 of the activated KDR/Flk-1 receptor as taught by Takashashi and Harlow et al. A kit will allow for ease of use for the practitioner since all the essential reagents, and standard for use are included in a kit as taught by the '011 patent (see col. 15, lines 54-61, in particular). From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

13. No claim is allowed.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

15. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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